REMARKS

1. Claim Status

Claims 39-73 are pending in the application. Claims 39-73 were finally rejected in the March 12, 2009 Office Action.

Applicant respectfully requests that the claim amendments presented herein be entered in the application as they place the application in a condition for allowance or, alternatively, in a better form for appeal. Applicant maintains for the reasons explained below that claims 39-73 as amended herein are allowable and should be passed to issue. Applicant addresses each of the Examiner's concerns in the sections which are presented hereinbelow.

2. Claims 57-64 Are Definite

The term "preferably" has been deleted from claim 57. Accordingly, claims 57-64 satisfy the definiteness requirement of 35 U.S.C. § 112, ¶ 2.

3. Claims 57-64 Satisfy Written Description

In the March 12, 2009 Office Action, the Examiner maintained her rejection of claims 57-64 under 35 U.S.C. § 112,¶ 1 for failure to satisfy written description on grounds that the specification of the application as originally filed, when coupled with the knowledge of those of ordinary skill in the art as of the filing date, did not support a claim to "reducing the likelihood of a recurrence of breast cancer". Applicant traverses these rejections and respectfully maintains that claims 57-64 satisfy written description for the following reasons.

Per the Examiner, a claim limitation "reducing the likelihood of a recurrence of breast cancer" implies that a treating physician must first determine that the patient "would in fact come out of remission if not treated." March 12, 2009 Office Action, p. 3. This is not correct. The limitation is directed to *reducing the likelihood* of a recurrence and does not imply that a treated patient would necessarily relapse absent treatment. As explained in the November 20, 2008 Amendment/Response, those of ordinary skill in the art as of the filing date, knew that the risk of relapse implicated factors such as diet,

estrogen levels, estrogen metabolites, and the existence of precancerous tissue by biopsy. Based on an analysis of such factors, a treating physician could reasonably reduce the likelihood of a relapse by applying the claimed methods without the need to determine that a relapse was a certainty absent treatment.

Additionally, per the Examiner, C. McNeil, *J. Nat. Can. Inst.,* 1998, 90(13):956-957 ("McNeil"); Jordan and Morrow, *Endocrine Reviews, 1999,*20(3), 253-278 ("*Jordan*"); V.C. Jordan, *J. Cell. Biochem. Supp.*1995, 22, 51-57 ("*Jordan (2)*"); and Olevsky and Martino, *Menopause*, 15, pp. 790-796 2008 ("*Olevsky*") do not evidence that a claim limitation to "reducing the likelihood of a recurrence of breast cancer" was supported in the specification as originally filed because the studies presented in those articles excluded patients who suffered from, or were suspected of having, breast cancer. This misapprehends the cited articles. *Jordan*, at page 258, notes that the nonsteroidal SERM Tamoxifen® provided a reduction in recurrence that was linked to duration of treatment; the portion of *Olevsky* (p. 268) cited by the Examiner related to the exclusion of cancer patients from a trial assessing the effect of raloxifene on fractures in post-menopausal women. *Olevsky, Jordan (2), and McNeil* do not contradict *Jordan's* clear indication that, as of the filing date, the class of compounds used in claims 57-64 could reasonably be understood to reduce the likelihood of a recurrence of breast cancer.

Accordingly, Applicant maintains that claims 57-64 satisfy the written description.

4. <u>Claims 39, 42, 65, 67, 68, and 70-73 Are Enabled</u>.

In the March 12, 2009 Office Action, the Examiner rejected claims 39, 42, 65, 67, 68, and 70-73 under 35 U.S.C. § 112, ¶ 1 for lack of enablement. According to the Examiner, those claims, while enabled for the treatment of osteoporosis and control of cholesterol levels, did not enable one of ordinary skill in the art to treat cardiovascular diseases in general.

Independent claims 39 and 65 have been amended to specify the treatment of cardiovascular diseases associated with elevated cholesterol or elevated low-density

lipoproteins (LDL). Support for these amendments is found in the specification as originally filed, e.g. at page 7, second and fifth paragraphs and in the Biological Examples. As of the filing date of the instant application, those of ordinary skill in the art understood that the estrogen receptor affinity and potency shown by the compounds used in the claimed methods reasonably predicted their utility in controlling cholesterol and LDL levels and in treating cardiovascular diseases such as atherosclerosis associated with elevated cholesterol or elevated LDL.

Applicant respectfully maintains that the amendment of claims 39 and 65 to specify the treatment of cardiovascular diseases associated with elevated cholesterol or elevated low-density lipoproteins (LDL) obviates the grounds of the Examiner's enablement rejection of claims 39, 42, 65, 67, 68, and 70-73 and that each of those claims satisfies the statutory enablement requirement.

5. <u>Claims 39-56 and 65-73 Are Nonobvious</u>.

In the March 12, 2009 Office Action, the Examiner maintained her rejection of claims 39-56 and 65-73 under 35 U.S.C. § 103(a) as being unpatentable for obviousness over U.S. Patent No. 3,972,906 ("*van den Broek*").

According to the Examiner, at the time of the invention of the pending claims, the use of *van den Broek's* estrogenic compounds to treat menopausal symptoms and breast cancer would have been obvious. Specifically, the Examiner asserts that:

> "[t]he obviousness rejection is proper as long as the prior art provides a reason and/or provides a motivation to use the prior art compounds as claimed by the instant claims. In the present case, van den Broek teaches the claimed compounds have estrogenic properties and, thus, are useful in treating estrogenic deficiency syndromes. The steroid art teaches the use of estrogenic agents in the treatment of menopausal syndrome such as osteoporosis as well as breast cancer. Therefore, the prior art provides the motivation to use the compounds of van den Broek in the claimed treatment methods.
> Lastly, similar compounds would be expected to have similar properties and, thus, even though the prior art does not teach the SERM activity of the prior art compounds said activity is inherent to the prior art compounds.
> March 12, 2009 Office Action, p. 8.

The bases of the Examiner's obviousness rejections are legally and factually inaccurate, as has been explained in Applicant's earlier submissions and as further clarified below.

The pending claims have been amended to clarify further that the compounds used in the claimed methods are selective estrogen receptor modulators (SERM's) which, as explained below, are used in a manner which is neither taught nor suggested by the prior art. Even though they are 11-substituted steroids, the compounds used in the claimed methods of treatment are antiestrogenic in the uterus, breast, and vagina, in contrast to the description of *van den Broek's* 11-substituted steroids, and are estrogenic in the liver and in promoting bone growth. *See* Specification, Biological Examples and Declaration of Dr. Richard Hochberg, ¶ 21.

Applicant's claimed methods represent the first use of steroidal SERM's:
(a) to treat menopausal symptoms in a patient while reducing the risk that the patient develops, or experiences a recurrence of, an estrogen-sensitive cancer;
(b) to treat an estrogen-sensitive cancer; and
(c) to reduce the likelihood of a reoccurrence of breast cancer in a patient.

At the time of the invention of the pending claims, the non-steroidal SERM Tamoxifen® was indicated for the treatment and prevention of breast cancer. It was recognized that post-menopausal patients treated with Tamoxifen® could benefit from a potential reduction in bone loss and cholesterol levels. Also, at the time of the invention of the pending claims, use of steroidal estrogen receptor modulators to treat post-menopausal symptoms was associated with an enhanced risk of breast cancer. The assertion in the March 12, 2009 Office Action that "[t]he *steroid* art teaches the use of estrogenic agents in the treatment of...breast cancer" (emphasis added) is simply incorrect.

There was no recognition in the prior art that a synthetic steroid could in fact treat menopausal symptoms while *lowering* cancer risk and without exacerbating preexisting cancer symptoms, *provided* the synthetic steroid exhibited SERM activity consistent with the compounds used in the claimed methods. Nor was there any understanding that a synthetic steroid could possess SERM activity and could therefore treat an estrogen-sensitive cancer or reduce the likelihood of a reoccurrence of breast cancer. These findings represented discoveries by the Applicant in the course of making the claimed invention.

Absent these discoveries of the Applicant prior to the present application, skilled artisans were not motivated to select *van den Broek's* 11-substituted steroids to treat patients in accordance with the presently claimed methods because they reasonably understood that *van den Broek's* 11-substituted steroids, while perhaps being effective in treating menopausal symptoms, could actually ***increase*** cancer risk. Therefore, based on what was known in the prior art and their own knowledge, those of ordinary skill in the art at the time of the invention of the pending claims would have reasonably believed that use of *van den Broek's* 11-substituted steroids would likely fail to achieve the purposes for which the currently claimed methods are administered. *See Takeda Chem. Indust. v. Alpharma Pty Ltd.*, 492 F.3d 1350; 2007 U.S. App. LEXIS 15349; 83 U.S.P.Q.2D (BNA) 1169 (Fed. Cir. 2007), *cert. denied*, 2008 U.S. LEXIS 3015 (U.S., Mar. 31, 2008) (no basis for skilled artisans to have selected primary obviousness reference compound for modification where one study showed that compound suffered from adverse effects).

From what was known about synthetic steroids and non-steroidal SERM's, those of ordinary skill in the art had no reason to expect that *van den Broek's* 11-substituted steroids would work for the purposes of the Applicant's claimed methods because, as explained above, they would have understood the estronergic activity identified by *van den Broek* to pose a cancer threat and they had no knowledge regarding potential SERM activity of 11-substituted steroids. *See Takeda* (no basis in prior art for skilled artisans to believe that substitution made by patentee would solve toxicity problem of primary obviousness reference compound).

Contrary to the Examiner's position, Applicant has not merely identified inherent aspects of methods of treatment disclosed or otherwise suggested by *van den Broek* or other references. Using synthetic steroids possessing SERM activity for the purposes for which Applicant's claimed methods are administered was not suggested by, and in fact was contrary to, the teachings of both the synthetic steroid art and the non-steroidal SERM art. *Cf. Rapoport v. Dement, et al.*, 254 F.3d 1053, 1059, 59 U.S.P.Q. 2d 1215 (Fed. Cir. 2001) (no inherent anticipation where prior art reference, although disclosing treatment of a related malady, did not describe purpose of the claimed methods).

In summary, the Examiner's obviousness rejection ignores both the purposes for

which the claimed methods are administered and the advantages of those methods, and further presupposes knowledge on the part of skilled artisans about the nature and properties of the administered compounds that could have only been gained from Applicant's invention. Such a hindsight reconstruction of the prior art is legally impermissible. *See Ortho-McNeil Pharma., Inc. v. Mylan Labs, Inc.*, 520 F.3d 1358, 86 U.S.P.Q.2d 1196 (Fed. Cir. 2008) (*KSR* posits a situation with a finite, and in the context of the art, small or easily traversed, number of options that would convince an ordinarily skilled artisan of obviousness; only by impermissible hindsight could patentee's selection and modification of a compound putatively developed for a different application be found obvious in this instance).

Accordingly, Applicant maintains that claims 39-56 and 65-73 are nonobvious over *van den Broek* and patentable.

For the above reasons, Applicants respectfully assert that the claims set forth in the amendment to the application of the present invention are now in compliance with 35 U.S.C. Applicants respectfully submit that the present application is now in condition for allowance and such action is earnestly solicited.

No fee is therefore due for the presentation of the amendments made herein. A petition for an extension of time is enclosed as is the requisite extension fee. Please charge any additional fee due or credit any overpayment to Deposit Account No. 04-0838.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: "Commissioner for Patents, P.O. Box 1450 Alexandria, Virginia 22313-1450" on August 12, 2009.

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